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09/857,448	06/04/2001	Patrick Midoux	USB98ASIDM	3117

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EXAMINER

SCHNIZER, RICHARD A

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/857,448

**Applicant(s)**

MIDOUX ET AL.

**Examiner**

Richard Schnizer, Ph. D

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 08 August 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 25,26 and 28-34 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 25,26 and 28-34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/8/05 has been entered.

Claims 20-24 and 35 were canceled as requested.

Claims 25, 26, and 28-34 remain pending and are under consideration in this Office Action.

All rejections from the previous Action which are not reiterated in this Action are withdrawn.

### ***Claim Objections***

Applicants amendments were sufficient to overcome the previous objections to claims 20, 30, and 33.

Claims 25 and 26 are objected to. At page 12 of the response Applicant indicates that these claims were amended to address formal matters. The Office assumes that the claims were amended to indicate the presence of a negatively charged carboxyl group at the right hand terminus of the conjugate. See pages 2 and 6 of the response. However, the PTO's electronic copies of pages 2 and 6 are of poor quality and contain a large number of black dots of approximately the same size as the

negative charge notation next to the carboxyl group. As a result it is unclear whether or not the amendment introduces a negative charge sign, or merely deletes the previous, ambiguous black line adjacent to the carboxyl group. Also, in the PTO's copy of the claims, the character 'n' in the first formula of each of claims 25 and 26 is illegible.

These claims also contain structures that are species of 'R' (see pages 3 and 7 of the response.) These structures contain subscripts  $n'$  and  $n''$ . However, in the structures themselves the prime and double prime designations are not in a subscript font. For example,  $(CH_2)_{n'}$  should be  $(CH_2)_{n'}$ , and  $(CH_2)_{n''}$  should be  $(CH_2)_{n''}$ .

A comma should be inserted in claim 25 after "q" at line 1 of page 4 of the response, and also in claim 26 after "q" at the penultimate line on page 7 of the response. (But see indefiniteness rejections below.)

Claims 30 and 31 are objected to because "conjugate" should be plural.

Claim 32 is objected to because "osteoblats" and "cancel" are misspelled, and because the word "cells" should follow the words "muscular", "epithelial", "endothelial", and "stem".

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25, 26 and 28-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25, 26 and 28-34 are indefinite because 'h' in claim 25 is ambiguous. This term is first defined as equal to "-H" (see page 5, line 6), then it is defined as "n being an integer from 1-6" at page 5, lines 7-19. So, on the one hand it is defined as an element (hydrogen), but on the other hand it is defined as a number. It is difficult to see how it could be both. Note that because 'h' is indefinite, the equations " $i = u + j + k + h$ " and " $j = f - (k + h)$ " at page 5 of the response are invalid.

The definition of 'u' at page 3, lines 5-10 of the response is confusing. As the Examiner understands the specification, 'u' is equal to the number of groups R that have any one of three structures listed in claim 25 at page 3, lines 8-10 of the response. This is not clear from claim 25. Claim 25 appears to define 'u' as a number and then separately as a structure. See page 3 lines 5-10 of the response. Perhaps line 6 of page 3 should be rewritten as "u is the number of groups R that is selected from the group" etc., if this is what Applicant intends and the specification provides support for it.

The claims are also confusing because the variables 'p' and 'q' have been redefined as chemical structures, whereas these variables were previously defined as numerical values. For example, p is redefined as  $\text{NH}_3^+$ , whereas it formerly was defined as a number that corresponded to  $\text{NH}_3^+$ . As a result, the equations in claim 25 on page 5 of the response that recite 'p' do not make sense. Perhaps the portion of claim 25 at the last line of page 3 of the response should be rewritten "R' represents  $\text{NH}_3^+$  or NH wherein NH is substituted by [a structure selected from the group listed at page 4 of the response], and wherein p is the number of R' groups that are  $\text{NH}_3^+$  groups, and q is the number of R' groups that are substituted NH groups; wherein the

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total number of R' groups is equal to  $p = q$ ". Again, this is dependent upon a showing of support in the specification. Note that this would also necessitate similar changes for variables  $p$  and  $q$  in claim 26.

The expression " $\text{NH}_3^+ = m = p + j + 1$ " in claim 25 at page 5 of the response appears invalid because  $p = \text{alpha NH}_3^+$ ,  $j = \text{omega NH}_3^+$ , and it is unclear to the Examiner that there is any type of  $\text{NH}_3^+$  in the claimed structure other than an alpha or omega  $\text{NH}_3^+$ , so it is unclear how the total  $\text{NH}_3^+$  can be the sum of alpha and omega  $\text{NH}_3^+$  plus 1. Where does the extra '1' come from?

### ***Response to Arguments***

Applicant's arguments filed 8/8/05 have been fully considered as they apply to the rejections set forth above, but they are not persuasive.

Applicant indicates at page 13 of the response a belief that the amendments overcome the rejections. However, there is no reason of record to believe that the expression " $\text{NH}_3^+ = m = p + j + 1$ " is valid, so the rejection is maintained for the reasons set forth above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***New Matter***

Claims 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 30-32 are drawn to methods of transferring oligonucleotides to cells that require the step of "treating said cell with" a composition of claim 25 in association with an oligonucleotide. This rejection concerns the scope of the term "treating" which was introduced into the claims by post-filing amendment on 1/20/04. The specification does not define this term, nor does it provide written support for the "treating" cells. Instead the specification provides support for contacting a composition of claim 25 with a medium comprising cells. See e.g. pages 25, 26, and 28, as well as the legends to Figures 1-3 at pages 30-33. The term "treating", given its broadest reasonable interpretation, embraces methods of delivering the composition to cells that do not require contacting said medium, i.e. one could deliver the composition as part of a particle used to bombard cells growing on a solid support, and from which the medium has been removed to facilitate particle bombardment. As a result, one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time the application was filed. Because the specification teaches examples in which cells are transfected with oligonucleotides through the use of compositions comprising the claimed conjugates in association with oligonucleotides

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 25, 26, 33, and 34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Midoux et al (WO 98/22610, published 5/28/98).

WO 98/22610 was filed as PCT/FR97/02022 and is the priority document for US Patent 6,372,499. The contents of WO 98/22610 will be discussed by reference to this English language version. Midoux teaches oligomers with a polymerization degree as low as 15, in which at least 10% of the monomers have free NH<sub>3</sub><sup>+</sup> groups substituted by residues that are protonable in a weak acid medium, such as histidines, pterines, quinolines, or pyridines, leading to destabilization of cell membranes. See entire document, e.g. abstract; column 4, lines 20-24; column 4, line 55 to column 5, line 40; column 6, line 48 to column 8, line 43; and column 10, line 44 to column 11, line 38. It is noted that the instant claims require at least 50% substitution. However, the recited "at least 10%" in the cited art is reasonably interpreted as embracing 10% to 100%, so the instantly claimed "at least 50%" is embraced by the range in the cited art. As such it would have been obvious to one of ordinary skill in the art to arrive at the claimed conditions through the process of routine optimization within the range in the cited art.



Note that the instant application shows that the instant invention functions to deliver polynucleotides when the level of substitution is 53%. See Table 1 on page 39.

Thus the invention as a whole was prima facie obvious.

### ***Response to Arguments***

Applicant's arguments filed 8/8/05 have been fully considered as they apply to the rejections set forth above, but they are not persuasive.

At page 14 of the response Applicant asserts that pending claims 28-33 are not subject to the obviousness rejection. This is incorrect. Claim 33 was rejected in the previous Action, and stands rejected in this Action.

In the paragraph bridging pages 14 and 15, Applicant indicates that they do not believe that there is motivation to select a degree of polymerization and a percentage of substitution of the prior art oligomers which would render obvious the instant claims because the present invention is appropriate for oligonucleotide transfection. This is unpersuasive because the prior art taught oligomers with a polymerization degree as low as 15, in which at least 10% of the monomers have free NH<sub>3</sub><sup>+</sup> groups substituted by residues that are protonable in a weak acid medium. Thus the prior art taught a polymerization value within the claimed range. Further, the degree of substitution is reasonably interpreted as embracing 10-100%, and so overlaps the claimed range of at least 50%. MPEP 2144 states "[i]n the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re

Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).”

At page 15 of the response Applicant argues that the degree of polymerization and a percentage of substitution were not recognized as result effective variables, and so would not have been obvious to optimize. This is unpersuasive because: 1) the cited art teaches a polymerization degree within the claimed range, thereby obviating the need for optimization of that variable, and 2) the cited art clearly shows that the percentage of substitution is a result effective variable because its variation affects transfection results, see e.g. Fig. 5 which shows that transfection efficiency generally increases with level of substitution.

At pages 15 and 16 Applicant reiterates the belief that there is no motivation to modify the teachings of the cited art to make the instantly claimed invention. This is unpersuasive for the reasons set forth above, i.e. because the range taught in the prior art overlaps the claimed range, so there exists a prima facie case of obviousness.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

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If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

A handwritten signature in black ink, appearing to read 'RSchnizer', with a long horizontal line extending to the right.

Richard Schnizer, Ph.D.